Modern Concepts of Cardiovascular Disease

Published monthly by the AMERICAN HEART ASSOCIATION

1790 BROADWAY AT 58TH ST., NEW YORK, N. Y.

DR. J. HAMILTON CRAWFORD, Brooklyn, *Editor*

DR. CHARLES A. POINDEXTER, New York, *Associate Editor*

Vol. XI October, 1942 No. 10

UNIVERSITY OF COLORADO
OCT 15 1942
SCHOOL OF MEDICINE
MEMORIAL LIBRARY

ARTERIOSCLEROSIS WITH SPECIAL REFERENCE TO CORONARY SCLEROSIS

Part I

The term arteriosclerosis is properly limited to chronic noninfectious lesions of arteries. Syphilitic, streptococcic, rheumatic, typhoidal, typhus and tubercular arteritis, polyarteritis nodosa and other forms of infectious arteritis, including primary thrombotic processes are, therefore, excluded. Also excluded are the arterial diseases in which spasm of nervous origin appears to be the primary cause, e.g., Raynaud's disease, thrombo-angiitis obliterans, acrocyanosis, erythromelalgia, etc. There remain three types of arteriosclerosis:

1. Mönckeberg's sclerosis, responsible for beaded and pipe-stem peripheral arteries, is of little importance clinically. It is marked by necrosis and calcification of the arterial media. The necrosis is accompanied by relaxation of the muscle and the media is calcified in the dilated position of the vessel. Narrowing of the lumen, most likely to cause clinical disturbances, is due to engrafted atherosclerosis, when it occurs.

2. Arteriolar sclerosis. Arteriolar lesions, most familiar in renal arterioles though occurring widely, include hyalinization of the intima, hypertrophy of the media and hyperplasia of the endothelium. Castleman[1] had opportunity to examine biopsy specimens of kidneys, taken during splanchnic sympathectomy operations. He found no arteriolar changes in some early cases and no progression of lesions in a second kidney biopsy specimen from a woman one year after sympathectomy, whose systolic pressure had been 245 before operation and normal since. These findings and notably the relief of pressure following operation suggest that arteriolosclerosis is not the cause but the effect of hypertension. This supports the thesis that hypertension is caused primarily by a pressor substance producing by renal ischemia. If long continued this results in nephrosclerosis and establishes a vicious circle. Stress is important in the localization of lesions of atherosclerosis. Fuller[2] from a study of lipoids in the kidney concluded that "Arteriolosclerosis of the kidney, without regard to whether it is primarily or secondarily related to parenchymal lesions, is essentially atherosclerosis." Whether this is true or not the relation of arteriolar sclerosis to atherosclerosis is close.

3. Atherosclerosis is responsible for most of the arteriosclerosis which is clinically significant, i.e., sclerosis of coronary, peripheral and cerebral vessels. It was first recognized as a separable disease by Virchow. It was given its contradictory name (literally mushy-hardness) by Marchand because of the soft fatty material in the lesions. Adami and Aschoff demonstrated that the fatty material was cholesterol esters. The Russian school produced atherosclerosis-like lesions in rabbits by feeding animal fats. Anitschkow and Chalatow[3] produced these lesions by feeding cholesterol. Their work was not accepted. The experimental disease was called, disparagingly, "the cholesterol disease of rabbits."

Aschoff revived the Virchow theory of the causation of the disease — in modified form. His theory is that wear and tear, from the pressure of the circulating blood, injures the arterial intima and gives rise to swelling of the deep intimal layers with degeneration. The intima has no circulation but depends for its nutrition on the diffusion of plasma from the blood in the lumen. Cholesterol esters present in the diffusing plasma are precipitated in the regions of swelling and degeneration in the form of droplets. These droplets are picked up by phagocytic cells of local origin which thus become lipoid (foam) cells. Aschoff's theory, supported by Ribbert, has been generally accepted. The disease was looked upon as a wear and tear process in which age was a dominant factor. The relation of the constantly present cholesterol esters to the lesion was regarded as having no significance.

Klotz,[4] almost alone, objected to the Aschoff thesis. His studies disclosed that in early lesions foam cells were already present, not in the deep layers of the intima, but in the subendothelial layer. There were no free esters and no evidence of swelling or degeneration of the intima. He believed that the Aschoff theory was based on the study of relatively advanced lesions in which free esters arose from the breaking down of foam cells, and that the degeneration which Aschoff described was secondary.

My studies support Klotz' findings. The earliest lesions are not visible to the naked eye and consist solely of foam cells in the subendothelial layer of the arterial intima. Even early visible lesions, though made up of more massive collections of lipoid cells, show no swelling or degeneration of the deep or other layers of the intima, and there are no free esters.

Atherosclerosis, whether human or experimental, cannot occur without visible cholesterol. Cholesterol is a necessary part of all animal cells. It is present in the cells in a combined nonvisible form. Visible cholesterol (polariscope) occurs normally in the adrenal cortex, in myelin sheaths, in the interstitial cells of the testicle and sometimes in corpora lutea. Apart from these tissues visible cholesterol is associated with disease. It is literally *excess cholesterol.* Excess cholesterol in adequate dosage over long periods will produce in rabbits cirrhosis of the liver, enlargement of the spleen and chronic nephritis[5] — a triad of lesions corresponding to those produced by Gye and Purdy[6] by intravenous injections of silica sol over long periods in rabbits. *Excess cholesterol* is therefore a *chronic irritant.* Like silica it provokes a growth of connective tissue.

There are two types of lesions of arteries asso-

ciated with the presence of cholesterol. The first type, *atheroma,* is a reversible process in youth, responsible for the aortic deposits in nurslings and at puberty, and in general for superficial lipoid deposits in the arteries of the young. The cholesterol esters appear in foam cells in the subendothelial layer of the intima as in true atherosclerosis. The excess cholesterol, however, is removed from the lesions by cells which have the character of fibroblasts.[7] In these the cholesterol esters are split, the excess cholesterol is dissolved and disappears from the lesion. The stay of the excess cholesterol, with its chronic irritant properties, is not long enough to provoke true atherosclerosis. As the body ages the power to remove excess cholesterol from the arteries is lost, except in the ascending aorta, where the power may persist into old age.

In the progressive process, *atherosclerosis,* the foam cells persist for long periods and the excess cholesterol stimulates a growth of connective tissue. In this way definite nodules are formed. As a nodule increases in size more and more cholesterol appears in new accretions of foam cells. Nutrition of the enlarged mass of cells by diffusion of plasma is no longer adequate. The deeper layers of the lesion undergo necrosis, and scarring occurs. In this manner typical nodular sclerotic lesions arise. In the aorta it has been possible to follow the evolution of lesions and to demonstrate the sequence from early to advanced processes.[7] In addition to typical orange, yellow, gray and white nodules, whose color is due to stages in this evolution, soft nodules arise which have only a thin endothelial covering. They are called atheromatous abscesses and are made up of masses of foam cells with inadequate supporting tissue and inadequate provision for nutrition. Necrosis of the foam cells occurs, setting free the cholesterol esters which split. The cholesterol thus freed crystalizes into solid rhombic plates which fuse into masses. The concentrated cholesterol prevents infection and there is no inflammatory exudate. A better name for this lesion is atherocheuma (mush liquefied). Rupture of an atherocheuma in the aorta is of minor significance since the contents are broken up in the whirling aortic current. Rupture produces pigmented foci due to hemorrhage into the lesion or, when the thin covering is torn away, so-called atheromatous ulcers arise, on which thrombi may form. Rupture of an atherocheuma into a coronary artery will produce occlusion (q.v.). Calcification of lesions is always a late monumental process.

Experimental atherosclerosis in the rabbit is produced by feeding cholesterol. In rabbits so fed there is a latent period of several weeks following the beginning of feeding before lesions appear in the aorta. By killing animals at critical intervals during this period I have been able to show that the ingested cholesterol is brought to the liver and esterified; that the esters collect in excess in the liver cells and the adrenals: that Kupffer cells in the liver and similar cells in the adrenals engulf the excess esters as particulate matter; that these ameboid cells, now become foam cells, escape from the organs through the blood and lymph streams, pass the so-called filter of the lungs with ease, and invade the aortic intima.[8] In this way atherosclerosis is produced.

The criteria accepted for demonstrating the causal relation of a bacterium to a disease are Koch's postulates. The bacterium must be constantly present in the lesions. It must be cultivated therefrom. When isolated in pure culture and injected into susceptible animals the lesions of the human disease must be reproduced. We have had to accept compromises in satisfying Koch's postulates in some infections because of cultural difficulties or lack of susceptible animals. Excess cholesterol ester crystals are as readily identifiable (polariscope) in tissues as are bacteria. They are constantly present in the lesions of atherosclerosis. Cholesterol can be extracted from the lesions, and when fed to rabbits in adequate amounts will lead to reproduction of the human lesions of the disease. No compromises with Koch's postulates are necessary. In order to study the late lesions it is necessary to permit experimental rabbits to live for years following cholesterol feeding. The reproduction of the lesions of human atherosclerosis is much more exact than is the reproduction of human lesions of many infectious diseases following the injection into susceptible animals of the accepted bacterial causes of those diseases.

Atherosclerosis belongs with diabetes, obesity and gout, a group of diseases due to inadequate metabolism of food substances and favored by excessive ingestion. There is a close linkage between diabetes and atherosclerosis. An inadequate carbohydrate metabolism seems to be accompanied by an inadequate cholesterol metabolism. Atherosclerosis in the diabetic does not differ from standard atherosclerosis in the method of its production or in the pathology of the lesions. It does tend to occur more frequently in youth, to develop more rapidly, and to be more serious in character in general. As in diabetes atherosclerosis may be a familial disease.

Atherosclerosis is closely related to thyroid functioning. Hyperthyroidism is associated with little or no atherosclerosis, hypothyroidism with advanced atherosclerosis. Thyroid extract fed in adequate amounts will modify or prevent the production of atherosclerosis in rabbits fed cholesterol.

Women mobilize cholesterol during pregnancy (for the use of the embryo?) and a minor mobilization occurs with menstruation. Apparently because of a more adequate cholesterol metabolism, perhaps related to this mobilization, women are less susceptible to coronary sclerosis than men, and tend to develop the disease later in life than men.

To summarize — Excess cholesterol is the cause of atherosclerosis. Stresses are important in determining the location and extent of the lesions. Age (time plus thyroid deterioration), sex and heredity are modifying factors.

Timothy Leary, M.D.
Boston, Mass.